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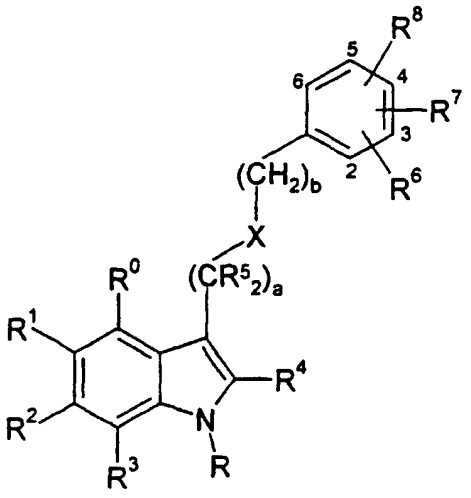
(54) Title: INDOLE DERIVATIVES



(I)

(57) Abstract: Compounds of formula (I) or salts or solvates thereof or physiologically functional derivatives thereof are potent binders at the EP4 receptor and are of use in the treatment or prevention of conditions such as a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder.

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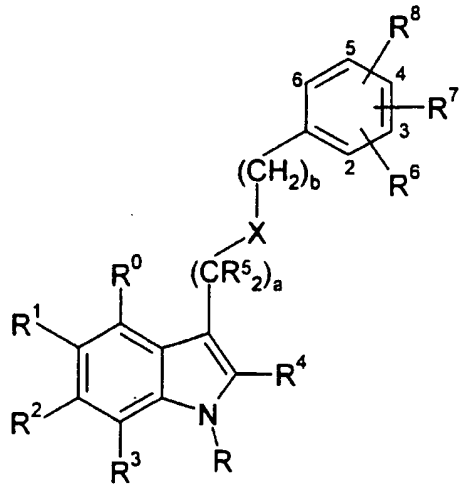
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INDOLE DERIVATIVES

This invention relates to indole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

The EP4 receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE_2. PGE_2 also has affinity for the other EP receptors (types EP1, EP2 and EP3). The EP4 receptor is associated with smooth muscle relaxation, inflammation, lymphocyte differentiation, bone metabolism processes, allergic activities, promotion of sleep, renal regulation and gastric or enteric mucus secretion. We have now found a novel group of compounds which bind with high affinity to the EP4 receptor.

The invention thus provides compounds of formula (I)



Formula (I)

or salts or solvates thereof or physiologically functional derivatives thereof in which:

a = 0, 1 or 2;

b = 0 or 1;

X is C(O)NR or NRC(O);

R is H or C_{1-4}alkyl;

R^0, R^1, R^2 and R^3 are each independently selected from H, halogen, C_{1-6}alkyl, SC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, OCH_2CF_3, O-cyclopropyl, OCH_2-cyclopropyl, NH_2, NHC_{1-6}alkyl, $N(C_{1-6}alkyl)_2$, NO_2, OH, CH_2OC_{1-6}alkyl, CH_2OH, arylC_{1-6}alkylenoxy, C_{1-6}alkyl-SO_2NH-C_{1-4}alkylene, aryl or heteroaryl;

R^4 is selected from H, C_{1-6}alkyl, aryl or heteroaryl;

each R^5 is independently selected from H, CH_3 or F;

R^6 is selected from SO_3H, SO_2NH_2, CH_2CO_2H, SO_2NHCOR, $CONHSO_2R$, $P(O)(OH)_2$, heteroaryl or C(O)Z where Z is OH or NR^9_2 where each R^9 is independently selected from H, C_{1-6}alkyl or $SO_2(CH_2)_c$aryl where c is 0 or 1;

R^7 is selected from H, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, NO_2, $CH=CHCO_2C_{1-6}$alkyl, $NHCOC_{1-6}$alkyl, C_{1-2}perfluoroalkyl, OH or CO_2R^{10} where R^{10} is selected from H or C_{1-6}alkyl; and

R^8 is H, or, when R^7 is C_{1-6}alkyl, C_{1-6}alkoxy or halogen, R^8 may also be C_{1-6}alkyl, C_{1-6}alkoxy or halogen; or

R^7, R^8 and the benzene ring to which they are attached are taken together to form a napthyl group or a benzene ring fused to a heteroaryl group; or

R^7 and R^8 are taken together to form a vicinal $OC(CH_3)_2O$ group.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof or a physiologically functional derivative thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water.

As used herein, the term "physiologically functional derivative" refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof. It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide physiologically functional derivatives thereof at any of the functional

groups in the compounds, and that the compounds of formula (I) may be so modified at more than one position.

It will be appreciated that, for pharmaceutical use, the "salt or solvate" referred to above will be a pharmaceutically acceptable salt or solvate. However, other salts or solvates may find use, for example, in the preparation of a compound of formula (I) or in the preparation of a pharmaceutically acceptable salt or solvate thereof.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Suitable pharmaceutically acceptable salts include acid addition salts formed from the addition of inorganic acids or organic acids, preferably inorganic acids. Examples of suitable acid addition salts include hydrochlorides, hydrobromides, sulphates and acetates. Further representative examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitirc acids. Suitable pharmaceutically acceptable salts also include alkali metal salts formed from the addition of alkali metal bases such as alkali metal hydroxides. An example of a suitable alkali metal salt is a sodium salt.

As used herein, the terms "alkyl" and "alkylene" (when used as a group or as part of a group) refer to a straight or branched hydrocarbon chain containing the specified number of carbon atoms. For example, C_{1-6}alkyl means a straight or branched hydrocarbon chain containing at least 1 and at most 6 carbon atoms. Examples of alkyl as used herein include, but are not limited to; methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of alkylene as used herein include, but are not limited to, methylene, ethylene, propylene and butylene.

As used herein, the term "perfluoroalkyl" (when used as a group or as part of a group) refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms wherein every hydrogen atom is substituted by a fluorine atom. For example, C_{1-2}perfluoroalkyl means a hydrocarbon chain

containing at least 1 and at most 2 carbon atoms wherein every hydrogen atom is substituted by a fluorine atom. Examples of perfluoroalkyl as used herein include trifluoromethyl and pentafluoroethyl.

As used herein, the terms "alkoxy" and "alkylenoxy" (when used as a group or as part of a group) refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms and having an oxygen atom attached to the chain. For example, C_{1-6}alkoxy means a straight or branched alkyl chain containing at least 1 and at most 6 carbon atoms and having an oxygen atom attached to the chain. Examples of alkoxy as used herein include, but are not limited to; methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy. Examples of alkylenoxy as used herein include, but are not limited to; methylenoxy, ethylenoxy and propylenoxy.

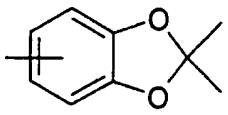
As used herein, the term "aryl" (when used as a group or as part of a group) refers to a phenyl or naphthyl group. Said aryl groups may be optionally substituted with one or more groups selected from C_{1-6}alkyl, C_{1-6}alkoxy, NO_2, hydroxyC_{1-4}alkylene, $CONH_2$, $CONH(C_{1-6}alkyl)$, $CON(C_{1-6}alkyl)_2$, halogen or phenyl. Where the aryl group is a phenyl group it may also be substituted so as to provide a methylenedioxyphenyl group.

As used herein, the term "heteroaryl" refers to a monocyclic five to seven membered aromatic ring. These heteroaryl rings contain one or more nitrogen, sulfur, or oxygen heteroatoms, where N-oxides, sulfur oxides and sulfur dioxides are permissible heteroatom substitutions. Examples of heteroaryl include furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine and pyrimidine. Said heteroaryl groups may be optionally substituted with with one or more C_{1-6}alkyl groups.

As used herein, the terms "halogen" or "halo" refer to fluorine, chlorine, bromine and iodine.

As used herein, the term "vicinal" when applied to a diradical group means that the free radical ends of the group are attached to adjacent carbon atoms on

another group. Thus a "vicinal $OC(CH_3)_2O$ group" attached to a phenyl group provides a group having the formula:



Certain compounds of formula (I) and certain salts or solvates or physiologically functional derivatives thereof may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or they may exhibit *cis-trans* isomerism). Each of the individual stereoisomers (including enantiomers and diastereomers) and all possible mixtures of these (including racemic mixtures) are included within the scope of the present invention. Likewise, it is understood that certain compounds of formula (I) and certain salts or solvates or physiologically functional derivatives thereof may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

In another aspect of the present invention, a is 1.

In another aspect of the present invention, b is 0.

In another aspect of the present invention X is C(O)NR.

In another aspect of the present invention, R is H or CH_3. Preferably R is H.

In another aspect of the present invention, R^0 is H, except when R^1 is H, in which case R^0 may be hydrogen or chlorine.

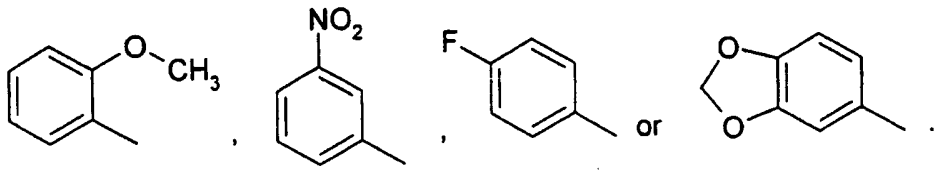
In another aspect of the present invention, R^1 is H.

In another aspect of the present invention, R^1 is C_{1-6}alkoxy. Preferably R^1 is methoxy.

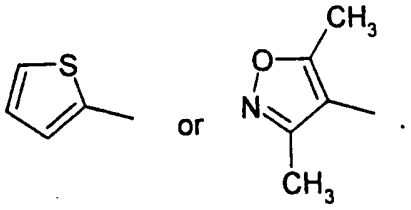
In another aspect of the present invention, R^1 is arylC_{1-6}alkylenoxy. Preferably R^1 is phenylC_{1-6}alkylenoxy, more preferably $PhCH_2O$.

In another aspect of the present invention, R^1 is halogen. Preferably R^1 is fluorine, chlorine or bromine.

In another aspect of the present invention, R^1 is aryl. Preferably R^1 is phenyl substituted with one substituent selected from C_{1-6}alkoxy (preferably methoxy), NO_2 or halogen (preferably fluorine); or phenyl substituted so as to provide a 1,2-methylenedioxyphenyl group. In particular, R^1 may be selected from:



In another aspect of the present invention, R^1 is heteroaryl. Preferably R^1 is thiophene or isoxazole optionally substituted with one or two C_{1-6}alkyl (preferably methyl) groups. In particular, R^1 may be selected from:



In another aspect of the present invention, R^2 is H, except when R^1 is methoxy, in which case R^2 is selected from H or methoxy.

In another aspect of the present invention, R^3 is H, except when R^1 is H, in which case R^3 is selected from H or phenylC_{1-6}alkylenoxy (preferably $PhCH_2O$).

In another aspect of the present invention, R^4 is H.

In another aspect of the present invention, R^4 is CH_3.

In another aspect of the present invention, R^4 is phenyl or phenyl substituted by a fluorine atom (preferably in the para position).

In another aspect of the present invention, each R^5 is H.

In another aspect of the present invention, R^6 is CO_2H.

In another aspect of the present invention, R^6 is tetrazole.

In another aspect of the present invention, R^6 is in the 2-position of the phenyl ring as those positions are numbered in formula (I) above.

In another aspect of the present invention, R^7 is H.

In another aspect of the present invention, R^7 is C_{1-6}alkyl. Preferably R^7 is methyl or ethyl, most preferably methyl. When R^7 is C_{1-6}alkyl it is preferably in the 4- or 5-position of the phenyl ring as those positions are numbered in formula (I) above. When R^7 is C_{1-6}alkyl it is most preferably in the 5-position of the phenyl ring as those positions are numbered in formula (I) above. Thus, in a particular aspect, R^7 is methyl in the 5-position of the phenyl ring as those positions are numbered in formula (I) above.

In another aspect of the present invention, R^7 is halogen. Preferably R^7 is fluorine, chlorine or bromine. When R^7 is halogen it is preferably in the 4-, 5- or 6-position of the phenyl ring as those positions are numbered in formula (I) above.

In another aspect of the present invention, R^7 is NO_2. When R^7 is NO_2 it is preferably in the 5-position of the phenyl ring as those positions are numbered in formula (I) above.

In another aspect of the present invention, R^7 is $CH=CHCO_2C_{1-6}$alkyl. Preferably R^7 is $CH=CHCO_2{}^tBu$. When R^7 is $CH=CHCO_2C_{1-6}$alkyl it is preferably in the 4-position of the phenyl ring as those positions are numbered in formula (I) above.

In another aspect of the present invention, R^7 is C_{1-2}perfluoroalkyl. Preferably R^7 is trifluoromethyl. When R^7 is C_{1-2}perfluoroalkyl it is preferably in the 5-position of the phenyl ring as those positions are numbered in formula (I) above.

In another aspect of the present invention, R^7 is OH. When R^7 is OH it is preferably in the 6-position of the phenyl ring as those positions are numbered in formula (I) above.

In another aspect of the present invention, R^8 is H, except when R^7 halogen, in which case R^8 is selected from H or halogen. When R^8 is halogen it is preferably in the 4-, 5- or 6-position of the phenyl ring as those positions are numbered in formula (I) above (and depending upon the position of R^7).

It is to be understood that the present invention covers all combinations of particular aspects of the invention as described hereinabove. In particular, the present invention covers the following combinations of particular aspects of the invention.

In another aspect of the present invention, there are provided compounds of formula (I) above or salts or solvates thereof or physiologically functional derivatives thereof in which:

a = 1;

b = 0;

X = CONR;

R is H;

R^0 is H;

R^1 is H;

R^2 is H;

R^3 is H;

R^4 is selected from H, Me or Ph;

R^5 is H;

R^6 is CO_2H in the 2-position of the phenyl ring as those positions are numbered in formula (I) above;

R^7 is in the 4-, 5- or 6-position of the phenyl ring as those positions are numbered in formula (I) above and is selected from H, C_{1-6}alkyl, halogen, NO_2, $CH=CHCO_2C_{1-6}$alkyl, C_{1-2}perfluoroalkyl or OH; and
R^8 is H, except when R^7 is halogen, in which case R^8 is in the 4-, 5- or 6-position of the phenyl ring as those positions are numbered in formula (I) above and is selected from H or halogen.

In another aspect of the present invention, there are provided compounds of formula (I) above or salts or solvates thereof or physiologically functional derivatives thereof in which:
a = 1;
b = 0;
X = CONR;
R is H;
R^0 is H;
R^1 is C_{1-6}alkoxy;
R^2 is selected from H or C_{1-6}alkoxy;
R^3 is H;
R^4 is selected from H, Me or Ph (which may be substituted by a halogen);
R^5 is H;
R^6 is in the 2-position of the phenyl ring as those positions are numbered in formula (I) above and is selected from tetrazole or CO_2H;
R^7 is in the 4-, 5- or 6-position of the phenyl ring as those positions are numbered in formula (I) above and is selected from H, C_{1-6}alkyl, halogen, NO_2, $CH=CHCO_2C_{1-6}$alkyl, C_{1-2}perfluoroalkyl or OH; and
R^8 is H, except when R^7 is halogen, in which case R^8 is in the 4-, 5- or 6-position of the phenyl ring as those positions are numbered in formula (I) above and is selected from H or halogen.

In another aspect of the present invention, there are provided compounds of formula (I) above or salts or solvates thereof or physiologically functional derivatives thereof in which:
a = 1;
b = 0;
X = CONR;

R is H;
R^0 is H;
R^1 is C_{1-6}alkoxy;
R^2 is selected from H or C_{1-6}alkoxy;
R^3 is H;
R^4 is selected from H or Me;
R^5 is H;
R^6 is CO_2H in the 2-position of the phenyl ring as those positions are numbered in formula (I) above;
R^7 is in the 4- or 5-position of the phenyl ring as those positions are numbered in formula (I) above and is selected from H, C_{1-6}alkyl, C_{1-2}perfluoroalkyl, halogen or NO_2; and
R^8 is H.

In another aspect of the present invention, there are provided compounds of formula (I) above or salts or solvates thereof or physiologically functional derivatives thereof in which:
a = 1;
b = 0;
X = CONR;
R is H;
R^0 is H;
R^1 is halogen;
R^2 is H;
R^3 is H;
R^4 is selected from H or Me;
R^5 is H;
R^6 is CO_2H in the 2-position of the phenyl ring as those positions are numbered in formula (I) above;
R^7 is in the 4-, 5- or 6-position of the phenyl ring as those positions are numbered in formula (I) above and is selected from H, C_{1-6}alkyl, halogen, NO_2, $CH=CHCO_2C_{1-6}$alkyl, C_{1-2}perfluoroalkyl or OH; and
R^8 is H, except when R^7 is halogen, in which case R^8 is in the 4-, 5- or 6-position of the phenyl ring as those positions are numbered in formula (I) above and is selected from H or halogen.

In another aspect of the present invention, there are provided compounds of formula (I) above or salts or solvates thereof or physiologically functional derivatives thereof in which:

a = 1;

b = 0;

X = CONR;

R is H;

R^0 is H;

R^1 is aryl;

R^2 is H;

R^3 is H;

R^4 is selected from H or Me;

R^5 is H;

R^6 is CO_2H in the 2-position of the phenyl ring as those positions are numbered in formula (I) above;

R^7 is in the 4-, 5- or 6-position of the phenyl ring as those positions are numbered in formula (I) above and is selected from H, C_{1-6}alkyl, halogen, NO_2, $CH=CHCO_2C_{1-6}$alkyl, C_{1-2}perfluoroalkyl or OH; and

R^8 is H, except when R^7 is halogen, in which case R^8 is in the 4-, 5- or 6-position of the phenyl ring as those positions are numbered in formula (I) above and is selected from H or halogen.

In another aspect of the present invention, there are provided compounds of formula (I) above or salts or solvates thereof or physiologically functional derivatives thereof in which:

a = 1;

b = 0;

X = CONR;

R is H;

R^0 is H;

R^1 is heteroaryl;

R^2 is H;

R^3 is H;

R^4 is selected from H or Me;

R^5 is H;
R^6 is CO_2H in the 2-position of the phenyl ring as those positions are numbered in formula (I) above;
R^7 is in the 4-, 5- or 6-position of the phenyl ring as those positions are numbered in formula (I) above and is selected from H, C_{1-6}alkyl, halogen, NO_2, $CH=CHCO_2C_{1-6}$alkyl, C_{1-2}perfluoroalkyl or OH; and
R^8 is H, except when R^7 is halogen, in which case R^8 is in the 4-, 5- or 6-position of the phenyl ring as those positions are numbered in formula (I) above and is selected from H or halogen.

In one aspect the invention provides the following compounds or salts or solvates thereof or physiologically functional derivatives thereof:
2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid,
2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid,
2-[(1H-indol-3-ylacetyl)amino]-4-methylbenzoic acid,
4-methyl-2-{[(2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid,
2-{[(5-fluoro-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid,
2-({[5-(benzyloxy)-1H-indol-3-yl]acetyl}amino)-4-methylbenzoic acid,
2-{[(5-bromo-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid,
2-{[(5-methoxy-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid,
4-bromo-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid,
4-fluoro-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid,
4-chloro-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid,
2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}-4-nitrobenzoic acid,
4-[(1E)-3-tert-butoxy-3-oxoprop-1-enyl]-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid,
5-chloro-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid,
4,5-difluoro-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid,
4-ethyl-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid,
2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}-5-methylbenzoic acid,
2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}-4-(trifluoromethyl)benzoic acid,
3-hydroxy-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid,
3,5-dichloro-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid,
2-{[(5,6-dimethoxy-2-methyl-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid,
2-{[(5-chloro-2-methyl-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid,

2-({[7-(benzyloxy)-1H-indol-3-yl]acetyl}amino)-4-methylbenzoic acid,
2-{[(4-chloro-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid,
4-methyl-2-{[(2-phenyl-1H-indol-3-yl)acetyl]amino}benzoic acid, and
2-{[(5,6-dimethoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid.

The compounds of the invention bind to the EP4 receptor and are therefore useful in treating EP4 receptor mediated diseases.

In view of their ability to bind to the EP4 receptor, the compounds of the invention are useful in the treatment of the disorders that follow. Thus, the compounds of formula (I) are useful as analgesics. For example they are useful in the treatment of chronic articular pain (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint strucure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

The compounds of the invention are particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and

are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) are also useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, polymyositis, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) are also useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases, diseases of abnormal platelet function (e.g. occlusive vascular diseases) or diseases associated with organ transplantation. The compounds of formula (I) are also effective in increasing the latency of HIV infection.

The compounds of formula (I) are also useful for the preparation of a drug with diuretic action.

The compounds of formula (I) are also useful in the treatment of impotence or erectile dysfunction.

The compounds of formula (I) are also useful in the treatment of bone disease characterised by abnormal bone metabolism or resorption such as osteoporosis (especially postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cacchexia, calculosis, lithiasis (especially urolithiasis), solid carcinoma, gout and ankylosing spondylitis, tendinitis and bursitis. In a further aspect, compounds of formula (I) may be useful in inhibiting bone resorption and/or promoting bone generation.

The compounds of formula (I) are also useful for attenuating the hemodynamic side effects of NSAIDs and COX-2 inhibitors.

The compounds of formula (I) are also useful in the treatment of cardiovascular diseases such as hypertension or myocardiac ischemia; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).

The compounds of formula (I) are also useful in the treatment of neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, ALS, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

The compounds of formula (I) are also useful in the treatment of neuroprotection and in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

The compounds of formula (I) are also useful in the treatment of tinnitus.

The compounds of formula (I) are also useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine.

The compounds of formula (I) are also useful in the treatment of complications of Type 1 diabetes (e.g. diabetic microangiopathy, diabetic retinopathy, diabetic neohropathy, macular degeneration, glaucoma), nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

The compounds of formula (I) are also useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cyrrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

Certain of the compounds of the invention have been shown to be potent and selective EP4 receptor antagonists. Accordingly, in a further aspect of the invention, there is provided the use of compounds of formula (I) and pharmaceutically acceptable derivatives thereof in the treatment of disorders ameliorated by EP4 receptor antagonism.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medecine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE_2 at EP4 receptors.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is ameliorated by EP4 receptor antagonism.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE_2 at EP4 receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is ameliorated by an EP4 receptor antagonist which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by the action of PGE_2 at EP4 receptors.

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment of a condition which is ameliorated by EP4 receptor antagonism.

According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment or prevention of a condition such as a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions,

solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The EP4 receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, rofecoxib, valdecoxib or parecoxib; 5-lipoxygenase inhibitors; NSAID's, such as diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; $5HT_1$ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; EP1 receptor ligands; EP2 receptor ligands; EP3 receptor ligands; EP1 antagonists; EP2 antagonists and EP3 antagonists. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with one or more further therapeutic agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

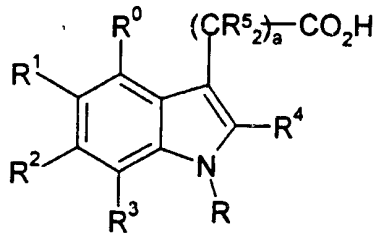
A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable salts for the treatment of man is from 0.01 to 10 mg/kg body weight per day and more particularly 0.1 to 3 mg/kg body weight per day, which may be administered as a single or divided dose, for example one to four times per day. The dose range for adult human beings is generally from 8 to 1000 mg/day, such as from 20 to 800 mg/day, preferably 35 to 200 mg/day.

The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

Compounds of formula (I) and salts and solvates thereof and physiologically functional derivatives thereof may be prepared by any method known in the art for the preparation of compounds of analogous structure.

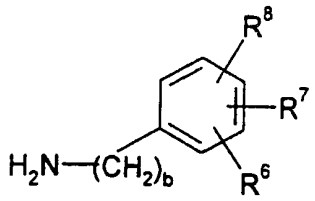
Compounds of formula (I) and salts and solvates thereof and physiologically functional derivatives thereof may be prepared by a process which comprises:

(A), coupling an acid of formula (II)



(II)

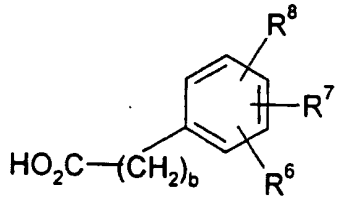
or a protected derivative thereof, with an amine of formula (III)



(III)

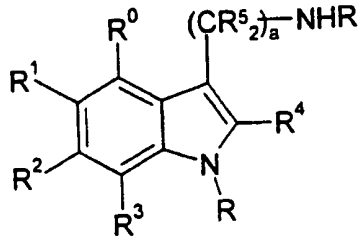
or a protected derivative thereof; or

(B), coupling an acid of formula (V)



(V)

or a protected derivative thereof, with an amine of formula (IV)



(IV)

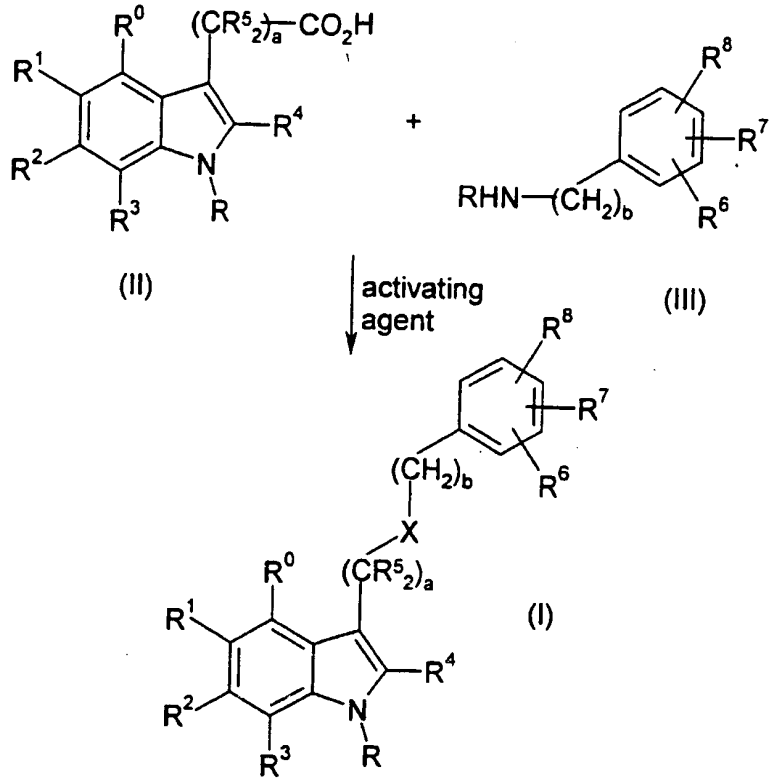
or a protected derivative thereof; or

(C), interconversion of a compound of formula (I) into another compound of formula (I); or

(D), deprotecting a protected derivative of compound of formula (I); and

optionally converting compounds of formula (I) prepared by any one of the processes (A) to (D) into a salt or solvate thereof or a physiologically functional derivative thereof.

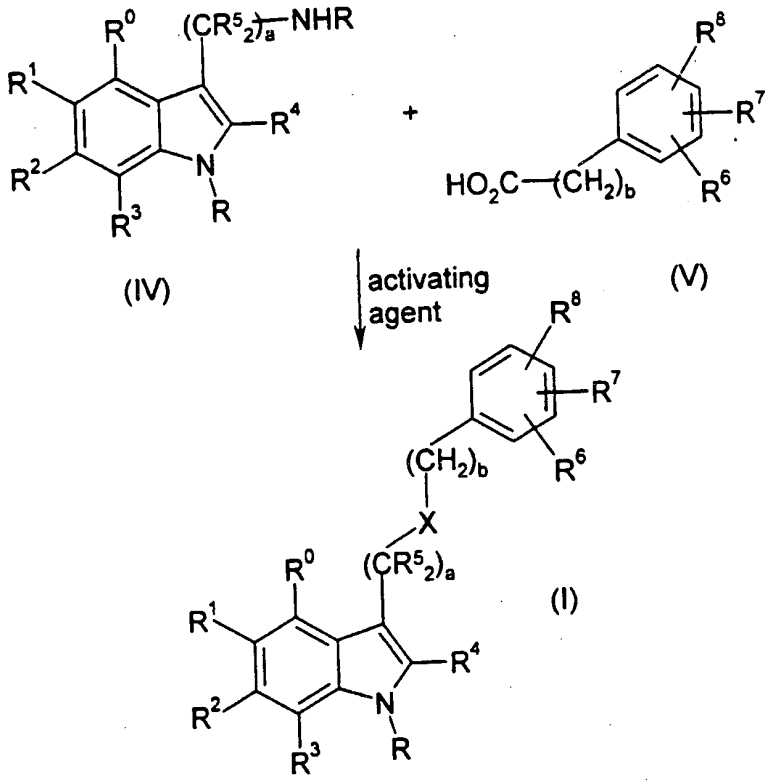
Suitable methods for the preparation of compounds of formula (I) and salts and solvates thereof and physiologically functional derivatives thereof are described below, and form a further aspect of the invention. In the Schemes that follow R to R^8, a, b and X are as defined in formula (I) above unless otherwise stated; CDI is 1,1'-carbonyldiimidazole, THF is tetrahydrofuran and DCM is dichloromethane.



Scheme 1

Referring to Scheme 1 above, compounds of formula (I) wherein X is C(O)NR may be prepared by coupling a compound of formula (II) with a compound of formula (III) in the presence of an activating agent, such as CDI, in a suitable aprotic solvent, such as THF or CDM. Such couplings are described in many organic texts such as 'Principles of Peptide Synthesis' by Miklos Bodanszky (Springer Verlag, 1984) chapter 2, incorporated herein by reference.

As shown in Scheme 2 below, compounds of formula (I) wherein X is NRC(O) may be prepared by coupling a compound of formula (IV) with a compound of formula (V) in an analogous manner to Scheme 1.



Scheme 2

Compounds of formulae (II) and (IV) are either known compounds or may be prepared by literature methods such as the Fischer Indole synthesis described in 'Advanced Organic Chemistry' by Jerry March, fourth edition (John Wiley & Sons, 1992) page 1141, incorporated herein by reference.

Compounds of formulae (III) and (V) are either known compounds or may be prepared by well known literature methods.

It will be appreciated by those persons skilled in the art that compounds of formulae (I) to (V) may be prepared by interconversion, utilising other compounds of formulae (I) to (V) as precursors.

As will be appreciated by those skilled in the art it may be necessary or desirable at any stage in the synthesis of any of the compounds of formulae (I) to (V) to protect one or more sensitive groups in the molecule so as to prevent undesirable side reactions. The protecting groups used in the preparation of compounds of formulae (I) to (V) may be used in conventional manner. See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W Green and Peter G M Wuts, second edition (John Wiley and Sons, 1991), incorporated herein by reference, which also describes methods for the removal of such groups.

Solvates (e.g. hydrates) or salts of a compound of the invention may be formed during the work-up procedure of any one of the aforementioned process steps.

The examples that follow illustrate the invention but do not limit the invention in any way. All temperatures are in °C. Liquid chromatography/mass spectrometry (LC/MS) was performed using a 3.3cm x 4.6mm ID, 3µm ABZ+PLUS column at a flow rate of 3ml/min and with an injection volume of 5µl at room temperature. The solvents used were 0.1% formic acid + 99.9% 10 mM ammonium acetate (solvent A) and 95% acetonitrile + 4.95% water + 0.05% formic acid (solvent B). The solvent gradient used is given in the table below. The mass spectrometer was a Micromass series II MS HP1050.

Time	A%	B%
0.00	100	0
0.70	100	0
4.20	0	100
5.30	0	100
5.50	100	0

Example 1:

2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid

5-Methoxy-2-methyl-3-indole acetic acid (1.32g, obtainable from Aldrich Chemical Co), carbonyldiimidazole (1.07g) and tetrahydrofuran (27ml) were stirred under nitrogen at room temperature for 30min. Methyl 4-methylanthranilate (1.00g) and pyridinium tosylate (3.62g) were added and the

mixture refluxed for 24h. After cooling, the solvent was removed *in vacuo* and the residue diluted with dichloromethane (200ml) and washed with 2M hydrochloric acid (50ml), 2M sodium hydroxide (50ml), water (50ml), brine (40ml) and dried ($MgSO_4$). Solvent removal *in vacuo* afforded methyl 2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}-4-methylbenzoaote (2.09g). LC/MS: T_R 3.52min, MH^+ 367.

Methyl 2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}-4-methylbenzoaote (0.916g), lithium hydroxide (0.600g), water (50ml) and tetrahydrofuran (50ml) were refluxed for 3h. After cooling, the tetrahydrofuran was removed *in vacuo* and the aqueous residue washed with ether (2x25ml) and then acidified with glacial acetic acid (1.6ml). The precipitated solid was filtered off, washed with water and dried *in vacuo* to afford the title compound (0.757g). LC/MS T_R 3.58min, MH^+ 353.

The following compounds were prepared in an analogous manner to Example 1:

Example No.	Compound Name	MH^+	MH^-	T_R (min)
2	2-[(1H-indol-3-ylacetyl)amino]-4-methylbenzoic acid	309	307	3.70
3	4-methyl-2-{[(2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid	323	321	3.73
4	2-{[(5-fluoro-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid		325	3.81
5	2-({[5-(benzyloxy)-1H-indol-3-yl]acetyl}amino)-4-methylbenzoic acid	415	413	4.10
6	2-{[(5-bromo-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid		385, 387	4.25
7	2-{[(5-methoxy-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid	339	337	3.54
8	4-bromo-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid	417, 419		4.36

Example 9:

4-methyl-2-{[(2-phenyl-1H-indol-3-yl)acetyl]amino}benzoic acid

2-Phenyl-3-indole acetic acid (0.166g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.127g) and 4-methylanthranilic acid (0.100g) in dichloromethane (20ml) were refluxed for 48h under nitrogen. The solvent was then removed and the residue purified using mass spectroscopy directed automated HPLC to afford the title compound (0.053g). LC/MS T_R 3.58min, MH^+ 384.

The following compounds were prepared in an analogous manner to Example 9:

Example No.	Compound Name	MH^+	MH^-	T_R (min)
10	4-fluoro-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid	357	355	3.76
11	4-chloro-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid	373, 375	371, 373	4.20
12	2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}-4-nitrobenzoic acid	384	382	4.27
13	2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid	339		
14	5-chloro-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid	373, 375		4.20
15	4,5-difluoro-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid	375		4.24
16	2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}-5-methylbenzoic acid	353		3.48
17	2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}-4-(trifluoromethyl)benzoic acid	407		4.43
18	3-hydroxy-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid	355		3.61
19	3,5-dichloro-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid	407, 409		4.11
20	2-{[(5,6-dimethoxy-2-methyl-1H-indol-3-	383		3.14

	yl)acetyl]amino}-4-methylbenzoic acid			
21	2-{[(5-chloro-2-methyl-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid	357, 359		3.91
22	2-({[7-(benzyloxy)-1H-indol-3-yl]acetyl}amino)-4-methylbenzoic acid	415		3.73
23	2-{[(4-chloro-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid	343, 345		3.62
24	2-{[(5,6-dimethoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid	368		2.98

Example 25:
4-[(1E)-3-tert-butoxy-3-oxoprop-1-enyl]-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid

3-Bromophthalic anhydride (58.74g, obtainable from TCI) was dissolved in methanol (200ml) and refluxed for 24h. After removal of the methanol *in vacuo*, the residue was azeotroped with toluene (250ml). To this residue was added toluene (300ml), triethylamine (180ml), diphenylphosphoryl azide (112ml) and the mixture heated at 80°C for 1.5h. Acetone (150ml) and water (100ml) were then added and the mixture warmed at 60°C for 3h. After dilution with ethyl acetate (1000ml) the mixture was washed with 1M aqueous sodum carbonate solution (2x500ml), brine (250ml) and dried ($MgSO_4$). Solvent removal *in vacuo* followed by purification on a 2.5kg Biotage eluting with 19.2:0.8 petroleum ether : ethyl acetate afforded methyl 4-bromoanthranilate (13.7g).

5-Methoxy-2-methyl-3-indole acetic acid (5g, obtainable from Acros), carbonyldiimidazole (4.44g) and tetrahydrofuran (120ml) were stirred at room temperature for 30min after which methyl 4-bromoanthranilate (5.24g) and pyridinium tosylate (13.69g) were added and the mixture refluxed for 14h. After diluting with dichloromethane (200ml), the residue was washed with 2M hydrochloric acid (200ml), 2M sodium hydroxide (200ml), water (200ml) and brine (200ml) and dried ($MgSO_4$). After solidifying by treatment with cyclohexane and ethyl acetate, the solid was triturated with ether to afford methyl 4-bromo-2-{[(5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl]amino}benzoate (6.54g), MH^+ 433, 435; MH^- 431, 433; T_R 3.67min.

To methyl 4-bromo-2-{[(5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl]amino} benzoate (20mg) was added palladium acetate (2mg), tri-*o*-tolylphosphine (3mg), *t*-butyl acrylate (33µl), triethylamine (32µl) and dimethylformamide (1ml). After heating at 110°C for 18h, the solvent was removed in vacuo and the residue diluted with dichloromethane (10ml) and washed with 5% citric acid (5ml). Purification by SPE eluting with dichloromethane, chloroform, and chloroform : ether mixtures afforded the title compound (5mg), MH^+ 465; MH^- 463; T_R 4.47min.

Example 26:

4-ethyl-2-{[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]amino}benzoic acid

To methyl 4-bromo-2-{[(5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl]amino} benzoate (108mg) was added tetraethyltin (53µl) (CAUTION - TOXIC), tetrakis(triphenylphosphine)-palladium (6mg) and toluene and the mixture refluxed for 6h. After solvent removal, purification of the faster eluting component by Biotage eluting with 4:1 p40-60 petroleum ether : ethyl acetate afforded a solid (34mg). To this material was added tetrahydrofuran (5ml), water (2ml) and lithium hydroxide (21mg). After reflux for 18h, the tetrahydrofuran was removed in vacuo and the product extracted with 3:2 dichloromethane : ethyl acetate. Purification by SPE gave the title compound (25.7mg) MH^+ 367; MH^- 365; T_R 3.70min.

Example 27:

2-{[(5-(thiophen-2-yl)-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid

2-{[(5-bromo-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid (product of example 6, 48mg), thiophene-2-boronic acid (17mg), tetrakis(triphenylphosphine)palladium(0) (12mg) was heated in a mixture of 2M sodium carbonate solution (0.5ml) and dimethoxyethane (0.5ml) for 18h at 80°C. The mixture was concentrated and diluted with DCM, then washed with 2N HCl for 1hr. The solvent was reduced and the residue purified by mass-directed automated HPLC to give the title compound (2mg). MH^+ 391.

The following compounds were prepared in an analogous manner to Example 27:

Example No.	Compound Name	MH^+
28	2-{[(5-(2-methoxyphenyl)-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid	415
29	2-{[(5-(3-nitrophenyl)-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid	430
30	2-{[(5-(4-fluorophenyl)-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid	403
31	2-{[(5-(3-methoxyphenyl)-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid	415
32	2-{[(5-(3,4-methylenedioxyphenyl)-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid	429
33	2-{[(5-(3,5-dimethylisoxazol-4-yl)-1H-indol-3-yl)acetyl]amino}-4-methylbenzoic acid	404

Biological Data

The ability of the compounds to bind to EP4 receptors may be demonstrated in the Human EP_4 Scintillation Proximity Assay.

Quantification of radioligand binding by scintillation proximity assay (SPA) is a long-established principle. Briefly, the affinity of compounds for a receptor is assessed by the specific competition between known quantities of radiolabelled ligand and compound for that receptor. Increasing concentrations of compound reduce the amount of radiolabel that binds to the receptor. This gives rise to a diminishing scintillation signal from SPA beads coated with membranes that bear the receptor. The signal may be detected with a suitable scintillation counter and the data generated may be analysed with suitable curve-fitting software.

The human EP_4 SPA assay (hereafter referred to as 'the assay') utilises membranes prepared from Chinese Hamster Ovary (CHO cells) infected with Semliki Forest Virus (SFV). Genetically engineered SFV-1 viral particles containing the genetic sequence of the human EP4 receptor were used to infect CHO cells resulting in expression of the receptor protein in cellular membranes.

Cells washed free of media are homogenised in a pH-buffered medium containing peptidase inhibitors. A suitable buffer is of the following composition: 50mM HEPES, 1mM EDTA, 25μg/ml bacitracin, 100μM leupeptin, 1mM PMSF, 2μM Pepstatin A, pH adjusted to 7.4 with KOH. Following removal of cell debris by a low-speed centrifugation, a pellet of membranes is prepared by a high-speed (48000g) centrifugation of the resulting supernatant. Membrane suspensions such as that described may be stored at -80°C until used.

For assay, membranes expressing human EP_4 receptors are diluted in a pH-buffered medium and mixed with SPA beads coated with a suitable substance to facilitate the adhesion of membranes to the beads. The concentrations of membrane protein and SPA beads chosen should result in SPA binding signal of at least 300 corrected counts per minute (CCPM) when tritiated radioligand at a concentration close to its K_d (affinity value) is combined with the mixture. Non-specific binding (nsb) may be determined by competition between the radiolabelled ligand and a saturating concentration of unlabelled ligand. In order to quantify the affinity of EP4 receptor ligands, compounds are diluted in a stepwise manner across the wells of a 96-well plate. Radioligand, compound, and unlabelled ligand are then added to a 96-well plate suitable for the measurement of SPA binding signals prior to the addition of bead / membrane mixture to initiate the binding reaction. Equilibrium may be achieved by incubation at room temperature for 120 minutes prior to scintillation counting. The data so generated may be analysed by means of a computerised curve-fitting routine in order to quantify the concentration of compound that displaces 50% of the specific radioligand binding (IC_{50}). The affinity (pK_i) of the compound may be calculated from the IC_{50} by application of the Cheng-Prusoff correction. Suitable reagents and protocols are: reaction buffer containing 50mM HEPES, 10mM $MgCl_2$, pH adjusted to 7.4 with KOH; SPA beads coated with wheatgerm agglutinin; 1.25nM [^{3}H]-prostaglandin E_2 as radioligand; 10μM prostaglandin E_2 as unlabelled ligand; a three-fold dilution series of compound starting at 10μM and ending at 0.3nM is adequate.

The ability of the compounds to antagonise EP4 receptors may be demonstrated in the [^{125}I]cAMP Scintillation Proximity Assay (hereafter referred to as 'the cAMP assay'). The cAMP assay utilises HEK-293 cells expressing the recombinant

human EP4 receptor, obtained from Receptor Biology, Inc. Beltsville, MD, USA. The cells were cultured in Dulbecco's Modified Eagle Medium – HAM F12 mix (DMEM-F12), containing 10% heat inactivated-foetal bovine serum (FBS) and 2mM L-glutamine. The cells were either passaged into fresh medium or used in an assay once 90% confluency as determined visually had been achieved.

The cells were harvested by treatment with Versene, re-suspended in fresh culture medium and plated out to yield approximately 10,000 cells per well of a 96-well plate for overnight culture in culture medium additionally supplemented with 3μM indomethacin. For assay, the culture medium was replaced with assay medium (DMEM-F12 containing 300μM isobutylmethylxanthine (IBMX) and 3μM indomethacin) and incubated for 30 minutes. Following this, antagonist was then added at various concentrations such that an entire agonist concentration-effect curve could be obtained in the presence of a single concentration of the antagonist. The antagonist was allowed to equilibrate with the cells for 30 minutes. Subsequently the cells were challenged with an agonist for 15 minutes. The reaction was stopped by the aspiration of the assay medium and the addition of ice-cold ethanol. All incubations were carried out at 37C in a 5% carbon dioxide atmosphere. Care was taken to ensure the constancy of IBMX, indomethacin and vehicle (DMSO) concentrations throughout. The amount of cAMP in each well was then determined by [^{125}I]cAMP scintillation proximity assay using a proprietary kit, obtained from Amersham, Buckinghamshire, UK, and according to the manufacturer's instructions.

Data from cAMP assays were expressed as pmol cAMP per well. A four-parameter logistic equation of the form:

$E=((Em.[A])^nH)/((EC_{50}^nH)+([A]^nH))$

was then fitted to E/[A] curve data in order to estimate maximum effect (Em), curve mid-point (EC50), and Hill slope (nH); other terms in the equation are effect (E) and concentration ([A]). Individual estimates of curve parameters were obtained from each curve. An empirical estimate of antagonist affinity (pA_2) could then be obtained using the following formula:

$pA_2 = \log ((EC_{50}^B/EC_{50}^A)-1)-\log[B]$

where EC_{50}^A is the midpoint of a control agonist concentration-effect curve in the absence of antagonist; EC_{50}^B is the midpoint of an agonist concentration effect

curve produced in the presence of a fixed concentration of antagonist; and [B] is the concentration of antagonist used. Estimates from individual experiments were then averaged to provide mean data. Quoted values are therefore the mean ± standard deviation (s.d.) of n separate experiments, each derived from a separate cAMP assay.

For the rigorous estimation of antagonist affinity values (pK_b) the method of Arunlakshana and Schild was employed. Briefly, the midpoint of agonist concentration/effect curves in the presence and absence of antagonist are used to calculate concentration ratios (CR). Linear regression is performed on a plot of (CR-1) against concentration of antagonist (-log[B]) in order to estimate the point of intersection with the concentration (-log[B]) axis and the slope of the line. If the slope of the regression does not differ significantly from unity then it may be constrained to 1.0. Under this latter circumstance, the point of intersection on the concentration axis represents the affinity (pK_b) of the antagonist.

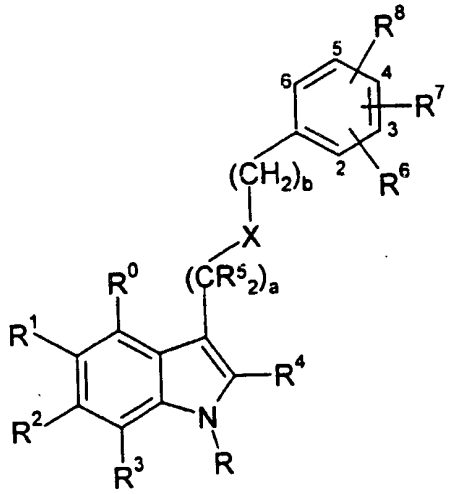
All of the compounds exemplified have a pK_i of 6.0 or greater at EP4 receptors as determined using the above-mentioned procedure:

The compounds synthesised in examples 1, 2, 3, 4, 6, 7, 9, 10, 11, 12, 13, 17, 20, 21 and 26 have a pK_i of 7.0 or greater at EP4 receptors as determined using the above-mentioned procedure.

The compound synthesised in example 1 has a pK_b greater than 8.0 at EP4 receptors as determined using the above-mentioned procedure.

Claims

1. Compounds of formula (I)



Formula (I)

or salts or solvates thereof or physiologically functional derivatives thereof in which:

a = 0, 1 or 2;

b = 0 or 1;

X is C(O)NR or NRC(O);

R is H or C_{1-4}alkyl;

R^0, R^1, R^2 and R^3 are each independently selected from H, halogen, C_{1-6}alkyl, S-C_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, OCH_2CF_3, O-cyclopropyl, OCH_2-cyclopropyl, NH_2, NHC_{1-6}alkyl, $N(C_{1-6}alkyl)_2$, NO_2, OH, CH_2OC_{1-6}alkyl, CH_2OH, arylC_{1-6}alkylenoxy, C_{1-6}alkyl-SO_2NH-C_{1-4}alkylene, aryl or heteroaryl;

R^4 is selected from H, C_{1-6}alkyl, aryl or heteroaryl;

each R^5 is independently selected from H, CH_3 or F;

R^6 is selected from SO_3H, SO_2NH_2, CH_2CO_2H, SO_2NHCOR, $CONHSO_2R$, $P(O)(OH)_2$, heteroaryl or C(O)Z where Z is OH or NR^9_2 where each R^9 is independently selected from H, C_{1-6}alkyl or $SO_2(CH_2)_c$aryl where c = 0 or 1;

R^7 is selected from H, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, NO_2, $CH=CHCO_2C_{1-6}$alkyl, $NHCOC_{1-6}$alkyl, C_{1-2}perfluoroalkyl, OH or CO_2R^{10} where R^{10} is selected from H or C_{1-6}alkyl; and

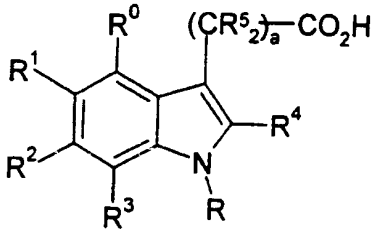
R^8 is H, or when R^7 is C_{1-6}alkyl, C_{1-6}alkoxy or halogen, R^8 may also be C_{1-6}alkyl, C_{1-6}alkoxy or halogen; or

R^7, R^8 and the benzene ring to which they are attached are taken together to form a napthyl group or a benzene ring fused to a heteroaryl group; or

R^7 and R^8 are taken together to form a vicinal $OC(CH_3)_2O$ group.

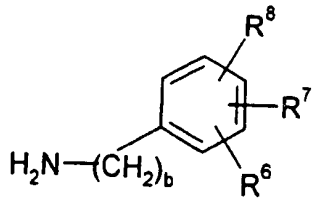
2. A process for the preparation of a compound of formula (I) or a salt or solvate thereof or a physiologically functional derivative thereof as defined in claim 1 which comprises:

(A), coupling an acid of formula (II)



(II)

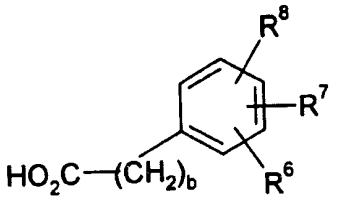
or a protected derivative thereof, with an amine of formula (III)



(III)

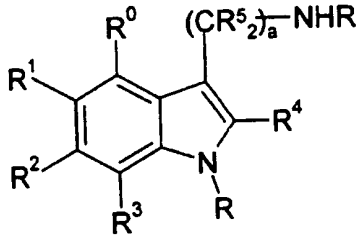
or a protected derivative thereof; or

(B), coupling an acid of formula (V)



(V)

or a protected derivative thereof, with an amine of formula (IV)



(IV)

or a protected derivative thereof; or

(C), interconversion of a compound of formula (I) into another compound of formula (I); or

(D), deprotecting a protected derivative of compound of formula (I); and

optionally converting compounds of formula (I) prepared by any one of the processes (A) to (D) into a salt or solvate thereof or a physiologically functional derivative thereof.

3. A pharmaceutical composition comprising a compound of formula (I) or a salt or solvate thereof or a physiologically functional derivative thereof as defined in claim 1 in admixture with one or more physiologically acceptable carriers or excipients.

4. A compound of formula (I) or a salt or solvate thereof or a physiologically functional derivative thereof as defined in claim 1 for use in human or veterinary medicine.

5. A method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE_2 at EP4 receptors, which method comprises administering to said subject an effective amount of a compound of formula (I) or a salt or solvate thereof or a physiologically functional derivative thereof as defined in claim 1.

6. The use of a compound of formula (I) or a salt or solvate thereof or a physiologically functional derivative thereof as defined in claim 1 for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by the action of PGE_2 at EP4 receptors.

7. A method of treating a human or animal subject suffering from a condition which is ameliorated by an EP4 receptor antagonist, which method comprises administering to said subject an effective amount of a compound of formula (I) or a salt or solvate thereof or a physiologically functional derivative thereof as defined in claim 1.

8. The use of a compound of formula (I) or a salt or solvate thereof or a physiologically functional derivative thereof as defined in claim 1 for the manufacture of a therapeutic agent for the treatment of a condition which is ameliorated by EP4 receptor antagonism.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/05701

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/18 A61P29/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 18744 A (HATTORI KOUJI ;KONO YUTAKA (JP); NAKAZATO SHOKO (JP); TANAKA AKIRA) 6 April 2000 (2000-04-06) page 1, line 11 -page 2, line 9; claims; examples	1-8
A	WO 00 21532 A (MERCK FROSST CANADA INC ;LABELLE MARC (CA); YOUNG ROBERT N (CA); M) 20 April 2000 (2000-04-20) page 1, line 9 -page 1, line 11 page 12, line 27 -page 13, line 34; claims 1-20	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2002	02/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Schmid, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/05701

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			EP	1148877 A1	31-10-2001
			WO	0021532 A1	20-04-2000
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			US	2001018433 A1	30-08-2001